Article

Evaluation of 21 426 feline bladder urolith submissions to the Canadian Veterinary Urolith Centre (1998–2014)

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Abstract — This study reports emerging trends in feline urolithiasis in Canada during the past 16.8 y, evaluates associations of breed and gender with urolith types, and reports on feline submissions from outside of Canada. Struvite and calcium oxalate uroliths comprised > 90% of all uroliths submitted. In cats, oxalate submissions outnumbered struvite submissions from Canada, Hong Kong, Denmark, and the United Arab Emirates, while Australian struvite submissions outnumbered calcium oxalate submissions. In Canada, the majority of urolith submissions were from domestic cats followed by Himalayan, Persian, and Siamese cats. Males were more likely to form calcium oxalate uroliths and females were more likely to develop struvite uroliths. Compared to domestic short-haired cats, Tonkinese, Burmese, Devon rex, Himalayan, Persian, and Siamese cats were significantly associated with calcium oxalate urolith submission. Egyptian mau, Birman, ocicat, and Siamese breeds were over-represented amongst urate submissions.

Résumé — Évaluation de 21 426 soumissions d'urolithes de vessie au Centre canadien d'urolithes vétérinaires (1998–2014). Cette étude présente un rapport sur les tendances émergentes pour l'urolithiase féline au Canada pendant les 16,8 dernières années, évalue les associations avec la race et le sexe pour les types d'urolithes et établit un rapport sur les soumissions félines provenant de l'extérieur du Canada. Les urolithes de struvite et d'oxalate de calcium représentaient > 90 % de tous les urolithes soumis. Chez les chats, les soumissions d'oxalate étaient supérieures aux soumissions de struvite pour les échantillons provenant du Canada, de Hong Kong, du Danemark et des Émirats arabes unis, tandis que les soumissions de struvite provenant de l'Australie étaient supérieures aux soumissions d'oxalate de calcium. Au Canada, la majorité des soumissions d'urolithes provenaient de chats domestiques suivis des chats himalayens, persans et siamois. Il était plus probable que les mâles aient des urolithes d'oxalate de calcium et il était plus probable que les femelles développent des urolithes de struvite. Comparativement aux chats domestiques à poil court, les chats tonkinois, burmese, Devon rex, himalayens, persans et siamois présentaient une association importante avec une soumission d'urolithes d'oxalate de calcium. Les races de chat Mau égyptien, birman, ocicat et siamois étaient surreprésentées parmi les soumissions d'urate.

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Introduction

Uroliths are a relatively common problem in cats, accounting for approximately 15% to 23% of all cases of feline lower urinary tract disease (FLUTD) (1–3). They are predominately found in the lower urinary tract, most specifically in the bladder. The two most common types of urolith identified in cats are struvite (magnesium ammonium phosphate hexahydrate) and calcium oxalate (4–8). The third most common type of urolith reported is ammonium urate or uric acid. Other types of urolith such as calcium phosphate, silica, xanthine, cystine, sodium pyrophosphate, and dried solidified blood clots are uncommon.

Risk factors for development of uroliths vary, including breed and gender predilections. Foreign shorthair, ragdoll, Chartreux, oriental shorthair, Himalayan, Persian, and Siamese cats have been associated with increased risk of struvite urolith formation (1,5,6,9–11), while Himalayan, Persian, Siamese, ragdoll, British shorthair, foreign shorthair, Havana brown, Birman, Chartreux, Scottish fold, and exotic shorthair cats have been associated with calcium oxalate uroliths (5,6,9–11). Egyptian mau, Birman,

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Siamese, Bengal, European shorthair, Havana brown, ocicat, oriental, ragdoll, rex, snowshoe, and Sphynx breeds have been associated with urate uroliths (12–14). Variable gender predispositions have also been reported (5–7,10–12,15).

Understanding associations is important for interpreting changing trends in urolithiasis and for investigating the pathophysiology of urolithiasis. The objectives of this study were to describe the composition of uroliths submitted from 1998 to 2014, to evaluate changes in urolith types over time, and to evaluate associations of breed and gender with urolith types.

Materials and methods

Data from all urinary bladder calculi from cats that were submitted to the Canadian Veterinary Urolith Centre (CVUC) between February 1, 1998 and November 30, 2014 were retrieved. Urethral plugs and uroliths from the upper urinary tract were excluded.

Urolith composition had been determined based on a standard series of assays. Briefly, each layer of each specimen was analyzed by optical crystallography, using polarized light microscopy. If additional clarification was needed, another quantitative technique was used, such as X-ray microanalysis, Fourier transformation infrared spectroscopy, or scanning electron microscopy. Uroliths containing at least 70% of a single mineral were classified as that mineral type. Uroliths composed of 2 mineral types in separate layers within the same urolith were classified as compound. Uroliths containing < 70% of a single mineral component and without an obvious nidus or surface layers were classified as mixed. Uroliths comprised of calcium oxalate monohydrate or calcium oxalate dihydrate or both were classified as calcium oxalate. Uroliths comprised of any of the salts of uric acid (ammonium, potassium, and sodium acid urate) were classified as urate. Calcium phosphates consisted of calcium phosphate apatite, calcium phosphate carbonate, and brushite. Animal data were obtained from questionnaires submitted with the uroliths.

Standard least squares fit was used to assess the change in proportion of individual urolith types over time. The association of breed and urolith type was evaluated using nominal logistic regression analyses for individual urolith types. Odds ratios and 95% confidence intervals (95% CI) were calculated for breeds for which a significant association was identified. The association between gender and urolith type was also evaluated using nominal logistic regression. A P-value < 0.05 was considered significant for all comparisons.

Results

A total of 21 426 feline cystoliths were submitted during the study period. Of these 20 183 (94.2%) were Canadian submissions, while 1243 (5.8%) were from outside of Canada.

Canadian submissions

Canadian feline submissions increased from 759 in 1998 (Feb to Dec) to 1483 submissions in 2014 (Jan to Nov). The top 3 submissions from cats from Canada were calcium oxalate (10 115/20 183; 50.1%), struvite (8071/20 183; 40%); and urate (893/20 183; 4.4%) (Table 1; Figure 1). Other urolith types, including cystine, xanthine, silica, calcium phosphate, potassium magnesium pyrophosphate, and dried solidified blood calculi (DSBC), were less commonly reported. There was a significant difference in the overall distribution of urolith types over time, with significant increases in the proportions of urate ($P = 0.003$), compound ($P = 0.002$) and mixed/other ($P = 0.001$) uroliths, along with a decrease in struvite ($P < 0.001$). There was no change in calcium oxalate or other urolith types over the study period. Changes in DSBC were not evaluated because this type was not specifically recorded until 2012.

Table 1. Canadian feline urolith submissions Februrary 1, 1998 to November 30, 2014

	Number of submissions	%
Calcium oxalate	10 115	50.1
Struvite	8071	40.0
Urates	893	4.4
Calcium phosphate	218	1.0
Silica	21	< 1
Xanthine	20	< 1
Cystine	16	< 1
Compound	205	1.0
Mixed	292	1.4
Other	332	1.6
Total	20 183	

Most (17 589/20 183, 87.1%) feline submissions came from domestic short-haired (DSH), medium-haired (DMH), and long-haired cats (DLH) (Table 2).

There were multiple associations between breed and oxalate, struvite, and ammonium urate uroliths (Table 2). Tonkinese, Burmese, Himalayan, Devon rex, Persian, and Siamese cats were predisposed to calcium oxalate uroliths compared with domestic short-haired cats. Domestic long-haired cats were more likely to form struvite stones than were domestic short-haired cats. Egyptian Mau, ocicat, Birman, and Siamese cats had higher predisposition to urate formation than did domestic short-haired cats. There were no breed associations for the remaining urolith types.

There were associations between gender and specific uroliths. Male cats were over-represented amongst calcium oxalate [odds ratio (OR): 1.73; 95% CI: 1.63 to 1.82; $P < 0.001$), urate (OR: 1.3; 95% CI: 1.16 to 1.54; $P < 0.001$), calcium phosphate apatite (OR: 1.83; 95% CI: 1.33 to 2.56; $P = 0.0002$), and DSBC (OR: 3.49; 95% CI: 1.28 to 12.2; $P = 0.013$) uroliths. Females were over-represented among struvite submissions (OR: 1.89; 95% CI: 1.78 to 2.00; $P < 0.0001$). There were no gender associations with the other urolith types.

International submissions

Submissions from outside of Canada began in 2009 (Hong Kong), and expanded in 2010 [Denmark, the United Arab Emirates (UAE), and Australia], and 2013 (Iceland). The majority of international submissions (981/1243; 78.9%) were from Hong Kong followed by Denmark (168/1243; 13.5%), the UAE (61/1243; 4.9%) and Australia (32/1243; 2.6%). There was only 1 submission from Iceland. Calcium oxalate was the most common type (778/1243; 62.6%), followed by struvite (372/1243;

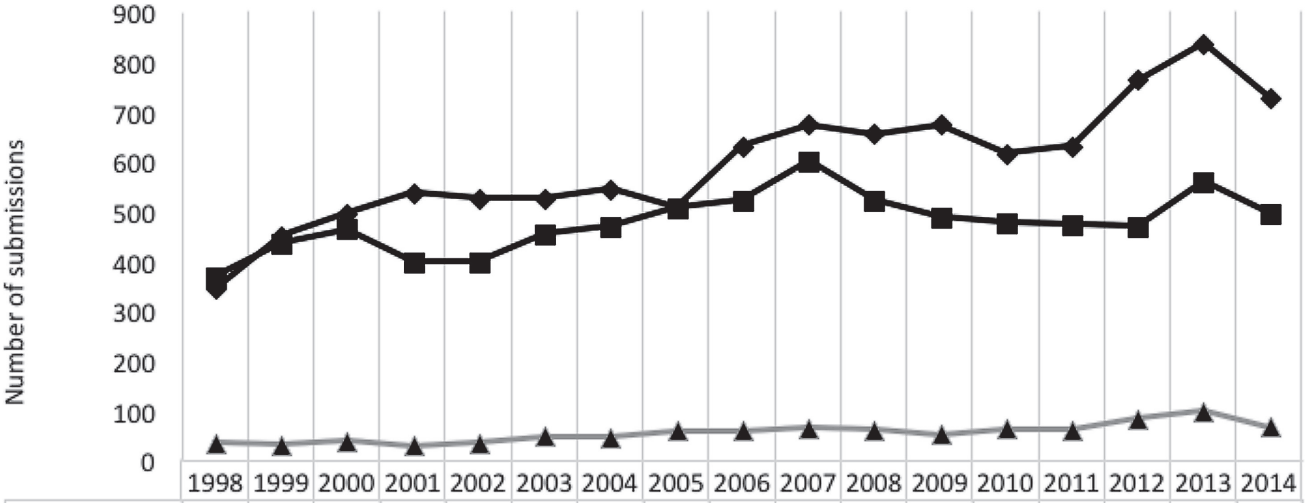

Figure 1. Changing trends in numbers of feline struvite, oxalate, and urate submissions in Canada from Feb 1, 1998 through to November 30, 2014.

Table 2. Significant associations between breed and urolith type among 20 183 urolith submissions from cats from Canada

Urolith type	Breed	Incidence	OR (95% CI)	*P*-value
Ammonium urate	Egyptian mau	20/25 (80%)	94.5 (38.2 to 285)	< 0.001
	Birman	8/28 (29%)	9.45 (3.91 to 20.8)	< 0.001
	Ocicat	7/16 (44%)	18.4 (6.55 to 49.5)	< 0.001
	Siamese	61/380 (16%)	4.52 (3.37 to 5.96)	< 0.001
	Domestic shorthair	598/14 336 (4.2%)	Ref	
Calcium oxalate	Himalayan	474/685 (69%)	2.7 (2.02 to 2.81)	< 0.001
	Persian	326/482 (68%)	2.21 (1.82 to 2.69)	< 0.001
	Siamese	225/380 (59%)	1.53 (1.25 to 1.89)	< 0.001
	Tonkinese	19/23 (83%)	5.02 (1.89 to 17.3)	0.0007
	Burmese	46/59 (80%)	3.74 (2.08 to 7.22)	< 0.0001
	Devon rex	25/36 (69%)	2.40 (1.21 to 5.09)	0.012
	Domestic shorthair	7073/14 336 (49%)	Ref	
Struvite	Domestic longhair	1293/2714 (48%)	1.31 (1.21 to 1.43)	< 0.001
	Domestic shorthair	5860/14 336 (41%)	Ref	

Ref — referent.

29.9%) (Table 3). Calcium oxalate was the most common urolith type submitted from Hong Kong (589/981; 60%), Denmark (137/168; 81.5%), and the UAE (40/61; 65.6%), while struvite submissions outnumbered oxalate submissions from Australia (18/32; 56% and 12/32; 38%, respectively) (Table 3). The number of submissions from outside of Canada were small so no further analysis was performed.

Discussion

While many urolith types were identified, calcium oxalate and struvite predominated. These 2 types have predominated in various other studies of urolith collections; however, there have been differences in the proportions of these types both between studies and over time. In the first year of investigation in this study, 48% of the submissions to the CVUC were struvite and 45% of the submissions were oxalate (16). Over time, the proportion of struvite uroliths declined, with a corresponding increase in oxalate submissions. In 1999, oxalate submissions to the CVUC surpassed struvite and that trend continued to 2004 (Figure 1) (5,16). In 2005, equal numbers of oxalate and struvite were recorded in Canada and since 2006, oxalate has remained the most common urolith submission from cats (Figure 1).

In the United States, 2 centers offering quantitative urolith analysis have published sequential data over the past 3 decades. A similar trend has been noted at the Minnesota Urolith Center (MUC) and the GV Ling Urinary Stone Analysis Laboratory (University of California — Davis). In the early to mid-1980s, calcium oxalate uroliths represented less than 5% of feline urolith submissions (6,8); however, calcium oxalate uroliths

Table 3. Gender and breed distribution of 20 183 uroliths from Canadian cat submissions between February 1, 1998 and November 30, 1998

Breed	Gender	Oxalate	Struvite	Urate	Other	Totals
Domestic cats (DSH, DMH, DLH) (17 589)	F	3489	4119	283	439	8330
	M	5054	3248	433	524	9259
Himalayan (685)	F	156	100	5	6	267
	M	315	83	4	13	415
	U	3				3
Persian (482)	F	99	70	6	9	184
	M	226	46	10	15	297
	U	1				1
Siamese (380)	F	66	35	23	10	134
	M	156	36	38	12	242
	U	4				4
Maine coon (89)	F	11	20	0	0	31
	M	29	26	1	2	58
Ragdoll (100)	F	20	16	2	1	39
	M	33	18	4	6	61
Burmese (59)	F	14	7	0	1	22
	M	32	2	1	2	37
Devon rex (36)	F	11	2	2	3	18
	M	14	1	1	2	18
Egyptian mau (25)	F	0	3	10	0	13
	M	0	1	11	0	12
Tonkinese (23)	F	7	1	0	1	9
	M	12	1	1	0	14
Breed not reported (713)	F	109	107	18	20	254
	M	158	62	25	32	277
Breed and gender not reported		97	67	15	2	181
Totals		10 118	8071	893	1100	20 183

F — female; M — Male; U — unknown.

accounted for approximately 50% of submissions by 1999 and struvite submissions slowly declined throughout the late 1980s and 1990s (8). A significant increase in calcium oxalate submissions was also reported in Germany, with an initial predominance of struvite (51.2%) but an increase in calcium oxalate over the 1981 to 2008 study period, with calcium oxalate surpassing struvite submissions in 2008 (48.6% *versus* 43.4%, respectively) (9).

In the present study, oxalate urolith submissions were the most common submission from Denmark, the UAE, and Hong Kong, while struvite submissions predominated only in Australia. Regional differences in urolith distribution have been reported in other studies, such as predominance of calcium oxalate submissions over struvite submissions in Africa, Germany, France, Switzerland, Belguim, the Netherlands, and Luxembourg (6,7,9,17).

The observed differences in the proportions of calcium oxalate and struvite uroliths over time and between countries may be related to factors such as signalment (age, gender, breed) of the cat, changes in health trends (e.g., obesity), climate, lifestyle, and diet (10,11,18,19), as well as differences in approaches to management of urinary tract disease.

A decrease in the proportion of struvite uroliths in our study was not surprising because of the relative ease of diagnosing struvite uroliths on survey radiographs and the efficacy and availability of diets that facilitate dissolution of struvite uroliths (20–22). The proper diagnosis and medical management of struvite uroliths should result in a decrease in submission of this urolith type, leading to an over-representation of uroliths that cannot be medically managed.

An association between domestic long-haired cats and struvite urolithiasis was identified and was unexpected. This has not been previously reported and a clear mechanism for this is not apparent.

Females were predisposed to struvite urolithiasis as has been previously published (5–7,10,11,15). Most struvite uroliths in cats are sterile so the anatomy of the urethra predisposing to urinary tract infection and struvite formation does not appear to be as important as it is in female dogs. Reasons why females are predisposed to sterile struvite stones more than males are not known and require further investigation.

The breed and male gender predispositions remain similar to those previously published, with the addition of a few new breed associations, likely because of the large sample size of this study. It is unclear why breeds such as the Himalayan, Persian, Siamese, Tonkinese, Burmese, and Devon rex account for disproportionately more oxalate submissions. There are reports in the literature alluding to long-haired breeds, which includes Himalayan and Persian cats, being at higher risk of idiopathic hypercalcemia, a condition known to cause hypercalciuria and

Table 4. Numbers of international feline stone submissions from 2009 to Nov 30, 2014

	Denmark	Australia	United Arab Emirates	Hong Kong	Iceland	Totals
Struvite	21	18	16	316	1	372
Oxalate	137	12	40	589	0	778
Urates	3	1	3	18	0	25
Cystine	0	0	0	4	0	4
Xanthine	0	0	0	5	0	5
Calcium phosphate	1	0	0	15	0	16
Silica	0	0	0	1	0	1
Mixed	2	1	0	17	0	19
Compound	2	0	1	8	0	11
Other	2	0	1	8	0	11
Total	168	32	61	981	1	1243

predispose cats to calcium oxalate uroliths (23). In certain dog breeds at increased risk of calcium oxalate urolithiasis, production of nephrocalcin, a substance in urine that naturally inhibits the formation of calcium oxalate uroliths, is believed to be defective, perhaps due to genetics (24). Whether such a defect exists in these breeds of cats is unknown.

Ammonium urate was the third most common urolith reported in cats. The Egyptian Mau, Birman, and Siamese breeds have been previously reported as predisposed (13). Ocicats were also identified as associated with urate uroliths. While the underlying genetic cause has been identified for urate stone formation in the Dalmatian and other canine breeds, a corresponding explanation in these cat breeds is lacking (25). Interestingly, the ocicat is a blend of Siamese, Abyssinian, and American shorthair cats; identification of related breeds that are associated with urolithiasis could help identify target genetic defects. Yet, the odds ratio for ocicats dwarfed that of their Siamese counterparts (18.4 *versus* 4.5), suggesting that simple relatedness to Siamese cats is not the explanation. Identifying reasons for this apparently elevated risk might help manage risk and, if a genetic marker is identified, this could facilitate development of selective breeding programs. Study of genetic defects in Egyptian mau cats, with their remarkable 94.5 odds ratio for urate urolithiasis, is also indicated. Males appear to be predisposed to urate uroliths, from both this study and previous reports (12–14).

The increase in calcium oxalate uroliths noted here and elsewhere cannot be taken as an indication of an increased incidence of oxalate urolithiasis since a change in the oxalate:struvite ratio does not mean that the incidence of oxalate urolithiasis has increased in the population. Incidence cannot be ascertained by a study such as this. There is also the potential for submission bias if veterinarians less commonly submit uroliths from predisposed breeds. However, this type of bias would be expected to dampen any identified risk factors, not result in spurious associations. Further, because uroliths are analyzed by the CVUC at no cost, there is less reason to suspect that there might be selective submission.

In conclusion, calcium oxalate and struvite uroliths remain the most common urolith submissions from cats, with oxalate predominating in Canada. Struvite submissions have significantly declined in Canada. Struvite uroliths are most often sterile and are readily amenable to medical dissolution. Gender and breed predispositions have been identified.

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Answers to Quiz Corner
Les réponses du test éclair

1. **A)** Hematuria at the end of urination is associated with lesions in the proximal urethra or bladder neck. The diagnosis is made via endoscopic examination of the urethra, during which a lesion is typically seen at the level of the ischial arch.

A) La présence d'hématurie à la fin de la miction est associée à des lésions de la portion proximale de l'urètre ou du col de la vessie. Le diagnostic est posé par examen endoscopique de l'urètre, durant lequel la lésion est observée au niveau de l'arcade ischiatique.

2. **B)** Idiopathic or interstitial cystitis is most common, with urolithiasis second.

B) La cystite idiopathique ou interstitielle est la plus commune, avec l'urolithiase en deuxième place.

3. **A)** *E. coli* is correct. *Staphylococcus* sp. cause less than half of infections. *Enterococcus* UTIs are increasing in frequency at referral hospitals in both dogs and cats but still make up considerably less than half of infections. *Enterobacter* and *Enterococcus* are very uncommon causes of UTI.

A) *E. coli* est correct. *Staphylococcus* sp. cause moins de la moitié des infections. La fréquence des infections du tractus urinaire par *Enterococcus* va en augmentant dans les hôpitaux spécialisés pour chiens et chats, mais la bactérie est responsable de beaucoup moins de la moitié des infections. *Enterobacter* et *Enterococcus* sont des causes très peu fréquentes d'infection du tractus urinaire.

4. **B)** The rate of rise in serum creatinine levels cannot be reliably predicted in an individual patient. In general, the prognosis for survival is longer in cats than in dogs. High systemic blood pressure has known adverse effects on patient survival and renal function. High PTH levels have adverse effects on survival and renal function, especially in dogs.

B) La vitesse de l'augmentation du taux de créatinine sérique n'est pas prévisible de façon fiable chez un individu. En général, le pronostic quand à la survie de l'animal est meilleur (survie plus longue) chez le chat que chez le chien. Une pression artérielle générale élevée a des effets secondaires fâcheux connus sur la survie des patients et la fonction rénale. Le taux élevé de la parathormone a des effets secondaires fâcheux sur la survie et la fonction rénale, spécialement chez le chien.

5. **E)** It is possible to correct many malpresentations by intrauterine manipulation, including lateral displacement of head and neck and shoulder flexion in anterior presentation, and breech presentation. Calves in posterior presentation are delivered in that position. Transverse presentations typically cannot be successfully delivered vaginally.

E) Il est possible de corriger plusieurs mauvaises présentations par manipulations intra-utérines, incluant le déplacement latéral de la tête et du cou, la flexion des épaules en présentation antérieure et la présentation du siège. La délivrance des veaux se fait normalement par présentation postérieure. Typiquement, les présentations transversales ne peuvent pas être corrigées avec succès par voie vaginale.